EXHIBIT K

CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Neonatal Opioid Withdrawal Syndrome

Stephen W. Patrick, MD, MPH, MS, FAAP,[a] Wanda D. Barfield, MD, MPH, FAAP,[b] Brenda B. Poindexter, MD, MS, FAAP,[c] COMMITTEE ON FETUS AND NEWBORN, COMMITTEE ON SUBSTANCE USE AND PREVENTION

The opioid crisis has grown to affect pregnant women and infants across the United States, as evidenced by rising rates of opioid use disorder among pregnant women and neonatal opioid withdrawal syndrome among infants. Across the country, pregnant women lack access to evidence-based therapies, including medications for opioid use disorder, and infants with opioid exposure frequently receive variable care. In addition, public systems, such as child welfare and early intervention, are increasingly stretched by increasing numbers of children affected by the crisis. Systematic, enduring, coordinated, and holistic approaches are needed to improve care for the mother-infant dyad. In this statement, we provide an overview of the effect of the opioid crisis on the mother-infant dyad and provide recommendations for management of the infant with opioid exposure, including clinical presentation, assessment, treatment, and discharge.

INTRODUCTION

The United States has experienced a surge in opioid use and opioid-related complications. From 1999 to 2009, there was a quadrupling of opioid pain reliever prescription sales nationwide.[1] By 2015, 3 times as many prescriptions for opioid pain relievers were filled than in 1999,[2] reaching >37% of US adults using opioid pain relievers in 2015.[3] The rapid increase in opioid pain reliever use in the early 2000s was associated with a parallel increase in opioid pain reliever–related treatment facility admissions and overdose deaths.[1] Since 2011, however, deaths from opioid pain relievers have plateaued, whereas deaths from heroin and fentanyl have grown exponentially.[4] In 2017, >47 600 Americans died of opioid-related overdoses (including opioid pain relievers, heroin, and fentanyl), outnumbering deaths from car crashes and firearms.[5]

As the opioid crisis grew in scope and complexity in the population at large, opioid use[6] and opioid use disorder (OUD)[7–9] among pregnant women also increased. Opioid use in pregnancy can lead to a withdrawal syndrome in the newborn shortly after birth. The syndrome has been traditionally called neonatal abstinence syndrome but more recently has been called neonatal opioid withdrawal syndrome (NOWS) by federal

abstract

[a]Division of Neonatology, Department of Pediatrics and Health Policy, School of Medicine, Vanderbilt University and Vanderbilt Center for Child Health Policy, Vanderbilt University Medical Center, Nashville, Tennessee; [b]Centers for Disease Control and Prevention, Atlanta, Georgia; and [c]Department of Pediatrics, College of Medicine, University of Cincinnati and Cincinnati Children's Medical Hospital Center, Cincinnati, Ohio

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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Address correspondence to Stephen W. Patrick, MD, MPH, MS, FAAP. E-mail: stephen.patrick@vanderbilt.edu

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agencies, including the US Food and Drug Administration.[10] Although neonatal abstinence syndrome is a more general term for neonatal withdrawal that, in the literature, may include nonopioid exposures (eg, benzodiazepines),[11] evidence suggests that the recent growth of neonatal drug withdrawal has been primarily from in utero opioid exposure either in isolation or in combination with other substances.[8]

The recent increase in OUD in pregnancy and NOWS reveals deficiencies in the continuum of care for the maternal-infant dyad in clinical and public systems. The child welfare system, for example, reported an increase of >10 000 infants in foster care from 2011 to 2017, most because of parental substance use.[12,13] Systematic, enduring, coordinated, and holistic approaches are needed to improve care for the mother-infant dyad. Optimizing the health and well-being of a pregnant woman gives her infant the highest likelihood of an ideal outcome. Care for the mother-infant dyad should be comprehensive and should consider the needs of both the mother and infant, as is outlined in the American Academy of Pediatrics (AAP) policy statement "A Public Health Response to Opioid Use in Pregnancy."[14] This statement builds on previous AAP-released clinical recommendations, including "Recommendations to the Indian Health Service on Neonatal Opioid Withdrawal Syndrome,"[15] and focuses primarily on the clinical presentation, assessment, and treatment of infants with opioid exposure and those with NOWS. The statement also discusses how the discharge process can be used to connect infants to important postdischarge services.

OUD IN PREGNANCY AND NOWS

Use of opioids, even as directed, can heighten risk of developing OUD, defined as a problematic pattern of opioid use that leads to clinically significant impairment or distress.[16] Rates of OUD in pregnancy grew substantially from 1999 to 2014,[7] with disproportionally higher rates in rural areas of the country.[9] Untreated OUD in pregnant women can result in dire consequences for the mother-infant dyad, including overdose death, fetal loss, and preterm birth. As highlighted by the recent report from the National Academies of Sciences, Engineering, and Medicine, "Medications for Opioid Use Disorder Save Lives,"[17] optimal care for pregnant women with OUD includes treatment with methadone or buprenorphine. Methadone is a full μ-opioid receptor agonist, which is dispensed from federally licensed opioid treatment programs. In contrast, buprenorphine is a partial μ-opioid receptor agonist and partial κ-opioid receptor antagonist that can be obtained from an opioid treatment program or from a provider who has obtained a waiver to prescribe through the Drug Addiction Treatment Act of 2000. Despite literature to support the use of medications for OUD in pregnancy, there remain substantial barriers in obtaining medications for OUD among pregnant women.[18,19] These barriers may, in part, be why the majority of pregnant women who are able to obtain treatment of OUD do not receive medications for OUD, despite evidence of their benefit.[18,20]

Opioid use typically does not occur in isolation and frequently involves other substances. In a recent study, using data from the National Survey of Drug Use and Health from 2005 to 2014, authors found that 5.1% of US pregnant women reported nonmedical use of an opioid pain reliever in the last year. Compared with pregnant women who did not report nonmedical use of an opioid pain reliever in the last 30 days, pregnant women who reported nonmedical use of an opioid pain reliever were more likely ($P < .001$) to also report last-30-day use of alcohol (49.2% vs 8.6%), tobacco (59.3% vs 15.6%), and marijuana (41.6% vs 3.3%).[21] Importantly, use of other substances (eg, tobacco)[22] or prescription sedatives (eg, benzodiazepines)[23] along with an opioid may increase risk and/or severity of NOWS. In addition, alcohol use in pregnancy is particularly problematic because alcohol, a teratogen, can cause fetal alcohol spectrum disorders and is the leading cause of preventable intellectual disability in the United States.[24] It is difficult for clinicians to disentangle the short- and long-term effects of exposure to opioids from other substances. Finally, social and economic factors,[25] systemic racism,[26] maternal physical and mental health, genetic and/or epigenetic, nutritional, and environmental factors may adversely affect infant development independent of maternal substance use disorder.[27]

Increases in maternal opioid use were accompanied by a parallel increase in NOWS.[8,9] From 2000 to 2016, the incidence of NOWS increased from 1.2 to 8.8 per 1000 hospital births.[8,28–30] These increases have been steeper in rural and tribal areas[9] and among infants enrolled in the Medicaid program.[29] In addition, there is remarkable state-to-state variation in NOWS. For example, West Virginia has the highest reported rate of NOWS at 33.4 per 1000 hospital births, compared with Hawaii at 0.7 per 1000 hospital births.[31] American Indian and Alaskan native populations have been disproportionately affected by NOWS. In 2016, American Indian and Alaskan native infants had the highest rate of NOWS at 15.9 per 1000 hospital births, compared with white infants at 10.5 per 1000 hospital births, Black infants at 3.4 per 1000 hospital births, and Hispanic infants at 2.5 per 1000 hospital births.[32]

ASSESSMENT AND CLINICAL PRESENTATION

Assessment of infants with opioid exposure by the health care team should include a thorough maternal history, including information gathered on substance use, additional medication use (prescribed and unprescribed), adversities experienced in childhood, cultural beliefs, trauma and violence exposures past and present, mental health disorders, and infectious diseases (including HIV and hepatitis C virus [HCV] infections). Ideally, clinicians should also assess the needs of the family, including the status of significant others and children as well as food and housing insecurity. When evaluating an infant with clinical signs consistent with NOWS, it is also important to consider other diagnoses that present similarly (eg, sepsis, hypoglycemia, hypocalcemia, and neurologic injury).

CLINICAL PRESENTATION OF NOWS IN NEONATES

NOWS occurs after chronic exposure to opioids (Table 1); therefore, exposure to opioids around the time of delivery, including opioids in an epidural or intravenous agonist and/or antagonist therapies (eg, nalbuphine, butorphanol), does not cause NOWS. The clinical presentation or risk of NOWS varies by opioid type (eg, immediate release, sustained release, maintenance),[22] the maternal drug history (including timing of the most recent use of drugs before delivery), maternal metabolism, net transfer of drugs across the placenta, placental metabolism, infant metabolism and excretion, and other factors.[11] In addition, maternal use of other substances, such as cigarettes, benzodiazepines, and gabapentin, may influence the onset, severity, or duration of the withdrawal syndrome.[22,23,33] Higher cumulative opioid exposure may increase the risk of NOWS among infants exposed to immediate-release prescription opioids[22]; however, studies of the relationship between maternal methadone[34,35] and buprenorphine[22,36] dosage and risk or severity of NOWS have generally found no relationship.

Because opioid receptors are concentrated in the central nervous system and the gastrointestinal tract, the predominant clinical signs reflect these systems (eg, tremors, loose stools; Table 2). Onset of clinical signs of withdrawal tend to reflect the half-life of the opioid involved. For example, withdrawal from heroin often begins within 24 hours of birth, whereas withdrawal from methadone usually begins at ~24 to 72 hours of age.[11] Withdrawal, however, may be delayed until 5 to 7 days of age, which is typically after hospital discharge for uncomplicated term infants.[11] Subacute signs of opioid withdrawal may last up to 6 months.[11,37]

SCREENING

Screening for substance use is distinct from testing for substance use. Screening generally refers to the use of a validated instrument to assess substance use, whereas testing refers to the use of a diagnostic test (eg, urine toxicology). Ideally, screening for substance use occurs in the first trimester by a prenatal provider (eg, family medicine, obstetrician, midwife) using a validated screening tool, as endorsed by the American College of Obstetricians and Gynecologists (ACOG). The ACOG recommends early universal screening for substance use at the time of the first prenatal visit.[38] During this time, other risks should be assessed, including HIV, HCV, and syphilis infection, and, if identified, appropriate planning for treatment (eg, HIV antiviral therapy) should occur in the perinatal period. An ACOG committee opinion mentions that screening tools include the "4 P's" for adults and the "CRAFFT" tool for adolescents (Table 3).[38] Clinical guidance from the AAP for screening

TABLE 1 Common Immediate-Release, Sustained-Release, and Maintenance Opioids

Drug	Immediate Release	Sustained Release	Maintenance
Buprenorphine	—	—	X
Codeine	X	—	—
Dihydrocodeine	X	—	—
Fentanyl	X	X	—
Hydrocodone	X	—	—
Hydromorphone	X	X	—
Levorphanol	X	—	—
Meperidine	X	—	—
Methadone	—	—	X
Morphine	X	X	—
Oxycodone	X	X	—
Oxymorphone	X	X	—
Tramadol	X	—	—

Adapted from Argoff CE, Silvershein DI. A comparison of long- and short-acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs. *Mayo Clin Proc.* 2009;84(7):602–612. —, not applicable.

TABLE 2 Signs of NOWS

Signs of NOWS
Central nervous system irritability
High-pitched, continuous crying
Decreased sleep
Tremors
Increased muscle tone
Hyperactive Moro reflex
Seizures
Gastrointestinal dysfunction
Feeding difficulties
Vomiting
Loose or watery stools
Autonomic nervous system activation
Sweating
Fever
Frequent yawning and sneezing
Increased respiratory rate
Nasal stuffiness and flaring

Adapted from Ko JY, Wolicki S, Barfield WD, et al. CDC Grand Rounds: public health strategies to prevent neonatal abstinence syndrome. *MMWR Morb Mortal Wkly Rep.* 2017;66(9):242–245.

adolescents for substance use can be found in the clinical report on substance use screening, brief intervention, and referral to treatment.[39] Prenatal clinicians can also use their state's prescription drug monitoring program as a resource for filled prescriptions because it may capture some high-risk patient behaviors, such as patients seeking controlled substances from different clinicians.[40] A complete summary of ACOG-recommended screening is beyond the scope of this statement but can be found online (https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Opioid-Use-and-Opioid-Use-Disorder-in-Pregnancy). Ideally, pediatric clinicians should work collaboratively with obstetric colleagues to obtain relevant clinical information (eg, screening results) to minimize care duplication. Pregnant women with OUD should also receive antenatal counseling by a pediatric health care provider to assess infant risks of NOWS and provide education on the clinical signs of withdrawal and need for nonpharmacologic and pharmacologic interventions.

SCREENING AND TESTING: MOTHER AND INFANT

Given the challenges in identifying infants at risk for NOWS with maternal screening, some have advocated for universal urine toxicology testing of mothers at the time of delivery. In a recent cohort study from a single center, the efficacy of a universal testing protocol for all mothers was assessed in a community hospital setting. In this study, 5.4% of pregnant women had a positive drug test result at the time of admission (3.2% were positive for opioids). Of the pregnant women with a positive urine drug test result for opioids, 20% had a negative risk-based screen result.[41] However, screening and testing processes are complex and have potential legal ramifications, and the AAP endorses informed consent for toxicology testing of pregnant women.[14] Notably universal testing has resulted in disproportionately higher child protective services referrals for Black women compared with white women[42,43] Pediatricians should be aware of and reduce institutional biases in implementing universal toxicology testing for infants, which could result in unequal consequences for mothers and infants on the basis of race, ethnicity, and/or socioeconomic status.

Toxicology testing for an infant can occur from multiple modalities, including urine, meconium, and umbilical cord tissue.[11] A urine sample should be collected as soon as possible after birth if the clinician is concerned because many drugs are rapidly metabolized and eliminated.[44–46] For example, after in utero exposure, opioids and their metabolites may no longer be detectable in an infant's urine after the first few days of life. Similarly, a positive urine screening result may only reflect recent exposure for most substances and may not reflect previous, more remote in utero exposure. Drugs that are excreted in the hepatobiliary system as well as drugs excreted by the fetal kidneys into the amniotic fluid are concentrated in meconium. Meconium testing provides a longer window of time throughout the pregnancy, beginning as early as 20 weeks' gestation, and is generally considered the gold standard for infant toxicology testing.[47–49] Meconium collection, however, can be labor intensive, requiring collection for several days, and does not reflect periods of abstinence close to delivery. Meconium must be collected before it is contaminated by nonmeconium stools (ie, after the infant receives colostrum or transitional milk, mature human milk, or formula). More recently, umbilical cord tissue testing has emerged as an alternative to meconium collection; given that umbilical cord tissue is readily available at the time of birth, it has logistic advantages to meconium collection.[49–53] Although some studies have suggested equivalence between meconium and umbilical cord tissue testing,[53] others studies have found the paired testing of meconium and umbilical cord tissue to be discordant.[54] Clinicians should be mindful of the differences in testing modalities when considering their needs for testing and work with their laboratories to determine the best testing modality in their setting.

Infant toxicology testing should be completed when it will inform clinical management. In some instances, testing of the infant provides no additional clinical information and would not be recommended. For example, for women in treatment for OUD who are closely monitored with frequent toxicology testing, meconium and/or umbilical cord tissue testing would not likely provide any additional clinical information if this information is readily available to the pediatrician. Testing can be helpful, however, when clinical details are lacking (eg, late or

TABLE 3 Screening for Substance Use

Screening for Substance Use
4 P's[a]
Parents: Did any of your parents have a problem with alcohol or other drug use?
Partner: Does your partner have a problem with alcohol or drug use?
Past: In the past, have you had difficulties in your life because of alcohol or other drugs, including prescription medications?
Present: In the past month, did you drink any alcohol or use any other drugs?
Any "yes" answer indicates that additional assessment is needed.
CRAFFT[b,c]
C: Have you ever ridden in a car driven by someone (including yourself) who was high or had been using alcohol or drugs?
R: Do you ever use alcohol or drugs to relax, feel better about yourself, or fit in?
A: Do you ever use alcohol or drugs while you are by yourself or alone?
F: Do you ever forget things you did while using alcohol or drugs?
F: Does your family or friends ever tell you that you should cut down on your drinking or drug use?
T: Have you ever gotten in trouble while you were using alcohol or drugs?
Two or more "yes" answers indicate that additional assessment is needed.

[a] Ewing H. A practical guide to intervention in health and social services with pregnant and postpartum addicts and alcoholics: theoretical framework, brief screening tool, key interview questions, and strategies for referral to recovery resources. Martinez, CA: The Born Free Project, Contra Costa County Department of Health Services; 1990.

[b] Notice to clinic staff and medical records: The information on this page is protected by special federal confidentiality rules (42 CFR §2), which prohibit disclosure of this information unless authorized by specific written consent. A general authorization for release of medical information is not sufficient.

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no prenatal care, placental abruption) and should be considered.

DIAGNOSIS, ASSESSMENT, AND TREATMENT

In the 1970s, several scoring systems were developed to guide the diagnosis and treatment of neonatal abstinence syndrome.[55,56] Still today, however, there is not one agreed-on scoring tool, and each scoring tool is prone to challenges of interrater reliability because each contains clinical signs that can be subjective or related to infant adaptation to extrauterine life.

The most commonly used scoring tool in the United States today is a modification of the original Finnegan score, developed in the early 1970s by Dr Loretta Finnegan.[55,57] Another commonly used score is a Finnegan scale modification created from the Maternal Opioid Treatment: Human Experimental Research (MOTHER) Neonatal Abstinence Measure trial (Fig 1).[58] Similar to other tools, the MOTHER modification includes common central nervous system, gastrointestinal tract, and autonomic clinical signs. Clinical signs are weighted to reflect severity; for example, sleeping <1 hour after feeding reflects a score of 3, whereas sleeping <3 hours after feeding reflects a score of 1. The score is used for initiation, advancement, and weaning of pharmacotherapy for NOWS on the basis of severity. The MOTHER modification suggests initiating pharmacotherapy if there is a consistent score of 9 to 12 or a single score of 13.

More recently, a new scoring tool has emerged, called Eat, Sleep, Console (ESC), which aims to guide treatment of NOWS.[59] The tool is guided by the infant's clinical signs of withdrawal through evaluation of an infant's ability to eat ≥1 oz or breastfeed well, sleep undisturbed ≥1 hour, and be consoled. If these criteria are not met, the medical team meets, assesses the environment and nonpharmacologic approaches, and considers initiating or escalating pharmacotherapy. ESC is appealing because of its ease of use and simplicity but has not been studied outside of quality improvement initiatives. It remains somewhat unclear, for example, if improvements in length of hospital stay are attributable to the ESC approach itself or to better adherence to nonpharmacologic approaches, which can also reduce length of stay.[59]

Despite challenges presented by scoring tools, data suggest that standardizing institutional scoring processes (ie, by using the same tool the same way with each patient) and training to improve interrater reliability improves clinical outcomes, including decreasing length of hospital stay.[60] For example, during the 2-year Vermont Oxford Neonatal Abstinence Syndrome Collaborative, standardized scoring processes were associated with a shorter length of stay (−3.3 days; 95% confidence interval [CI], −4.9 to −1.4).[60] The AAP does not endorse one scoring system over another because there is not significant evidence to support one tool's superiority. However, given evidence to suggest that establishing a consistent protocol and approach to scoring improves outcomes, every hospital should have a written protocol and optimize provider adherence. More research to support the optimal assessment of an infant with opioid exposure is needed.

CLINICAL MANAGEMENT OF NOWS

Observation

All infants with chronic opioid exposure should be observed for at least 72 hours to monitor for the development of withdrawal. Although

Appendix Figure 2. Maternal Opioid Treatment: Human Experimental Research (MOTHER) Neonatal Abstinence Measure

PATIENT ID#_____

Dose given q 3-4 hrs with feeds; do not exceed 4 hrs between doses

SCORE Morphine (0.04mg/0.1ml) DOSE FOR INITIATION

0-8	0	
9-12	0.04	mg/dose
13-16	0.08	mg/dose
17-20	0.12	mg/dose
21-24	0.16	mg/dose
25 or above	0.20mg/dose	

Morphine Initiation:

- If neonate scores 9-12 re-score after feeding or within the hour and if re-score is 9-12 start treatment based on highest score. If re-score is 0-8, do not initiate treatment.
- If initial score is 13 or greater, start treatment immediately without reassessment.

Morphine Maintenance

- Maintain dose if score 0-8
- Increase dose by 0.02 if score is 9-12 (rescore before dosing)
- Increase dose by 0.04 if score 13-16
- Increase score by 0.06 if score 17-20

Weaning Instructions:

- Maintain on dose 48 hrs before starting weaning
- Wean 0.02 mg morphine every day for a score is 0-8
- Defer wean for score e 9-12

Re-escalation

- If neonate scores 9-12 re-score as described for initiation .
- If second score is in 9-12 increase morphine 0.01 mg q3-4 hrs
- If 2 consecutive scores 13-16, increase 0.02 mg q3-4 hrs
- If 2 consecutive scores in 17-20, increase 0.04 mg q3-4 hrs etc

Timing of Scoring: Hospitalized infants scored every 3-4 hrs **before** feeds. Reassessment Occurs immediately **after feeds** or within 1 hour.
Discharged (e.g., in GCRC) infants scored twice a day scores must be separated by 8 hrs)
NOTE: Discharged infants are to be admitted to hospital if the infant receives a single score of 9 or more

SIGNS AND SYMPTOMS Please note **presence (pr) or absence (ab)** of items where indicated. Include observations for the past 4 hour period.	Score	Date/time	Date/time	Date/time	Date/time	Date/time	Date/time	Date/time	Date/time
Crying: excessive high pitched Crying: Continuous high pitched	2 3								
Sleeps < 1 hour after feeding Sleeps < 2 hours after feeding Sleeps < 3 hours after feeding	3 2 1								
Hyperactive Moro Reflex Markedly Hyperactive Moro Reflex	1 2								
Mild Tremors: Disturbed Moderate-Severe Tremors: Disturbed	1 2								
Mild Tremors: Undisturbed Moderate-Severe Tremors: Undisturbed	1 2								
Myoclonic jerks	present/absent	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab
Increased Muscle Tone	1-2								
Excoriation (indicate specific area):	1 - 2								
Mottling	present/absent	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab
Generalized Seizure (or convulsion)	8								
Convulsions	present/absent	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab
Fever ≥ 37.3 C (99.2 F)	1								
Fever >38.4 (101.2 F)	present/absent	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab
Frequent Yawning (4 or more successive times)	1								
Sweating	1								
Nasal Stuffiness	1								
Sneezing (4 or more successive times)	1								
Tachypnea (Respiratory Rate> 60/min)	2								
Retractions	present/absent	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab
Nasal flaring	present/absent	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab
Poor Feeding	2								
Excessive sucking	present/absent	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab
Vomiting (or regurgitation)	2								
Projectile vomiting	present/absent	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab
Loose Stools	2								
Watery Stools	present/absent	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab	☐pr ☐ab
Failure to Thrive (Current weight ≥ 10% below birth weight) 90% BWT=_____	2 (record weight in score box 1 x day)								
Excessive Irritability	1 - 3								
TOTAL SCORE									
CURRENT MORPHINE DOSE	Dose in mg Time Given								
STATUS OF TREATMENT*	N, I, M, W, R								
INITIALS of SCORER									

Note: Code Status of Treatment as follows: N="No treatment", I="Initiation", M='Maintenance", W="Weaning", R=' Re-Escalation"

FIGURE 1

MOTHER Trial Modification of the Finnegan Score. (Reprinted with permission from Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med.* 2010;363(24):2320–2331.)

there is increasing evidence that multiple factors may increase an opioid-exposed infant's risk of withdrawal (eg, gestational age, specific genotypes, cigarette use, benzodiazepine and gabapentin use), there remains insufficient evidence of how to use these exposures to tailor an infant's postnatal observation period. Institutions should consider observing infants exposed to immediate-release opioids for at least 3 days, infants exposed to buprenorphine and sustained-release opioids for 4 to 7 days, and infants exposed to methadone for 5 to 7 days. Notably, however, there remains limited evidence to inform observation periods, and excess observation could result in separation of the mother-infant dyad. Additional research is needed to inform appropriate hospital observation periods for infants with opioid exposure.

Setting

Traditionally, NOWS in the United States has been managed in the NICU[61]; however, many infants at risk for or with NOWS do not need NICU-level care. Depending on the physical design of the unit, care in a NICU may result in separation of the mother-infant dyad, which can further exacerbate infant clinical signs of withdrawal and can be traumatic for mothers during this vulnerable postpartum period. In addition, for infants going through withdrawal, the NICU environment, which can be loud and overly stimulating, may not be optimal. Recently, models of care have emerged that are focused on enabling the new mother to "room-in" with her newborn (in many cases, outside the NICU environment).[62] In a recent meta-analysis, it was found that rooming-in was associated with lower rates of pharmacotherapy for withdrawal (relative risk, 0.37; 95% CI, 0.19 to 0.71; I^2, 85%) and shorter lengths of hospital stay (weighted mean difference, –10.41 days; 95% CI, –16.84 to –3.98 days; I^2, 91%).[63] Keeping the mother-infant dyad together may promote bonding and facilitate breastfeeding, and rooming-in should be considered the preferred model, including in the NICU, for infants with opioid exposure. In addition, the environment and infant handling should be modified so that it is not overly stimulating, which can exacerbate clinical signs of withdrawal (eg, loud noises, bright lights). In addition, it is important that care clinicians (eg, nurses, nurse practitioners, physicians) cluster care interventions together temporally so as not to unnecessarily disturb the infant, which may also aggravate signs of withdrawal.

Nonpharmacologic Care

The literature to support specific nonpharmacologic approaches is sparse; however, evolving evidence suggests that effective nonpharmacologic care that engages the mother is an essential foundation to the care of an infant with opioid exposure. Nonpharmacologic care that is individualized should be applied beginning at birth for all infants with substance exposure and continued throughout hospitalization and beyond, regardless of the need for pharmacotherapeutic intervention. Engaging and coaching caregivers in nonpharmacologic care promotes bonding and may improve outcomes, beginning with education about the infant-specific signs of NOWS and helping the family to interpret what triggers the clinical signs the infant is experiencing and education about how to support his or her regulation. Clinical features of NOWS, such as irritability, uncontrolled movements, and fragmented sleep, can be challenging for the new mother. Providing support to the mother as she responds to these clinical features is important. Mothers frequently experience overwhelming feelings of guilt and anxiety in response to the dysregulated neurobehaviors associated with NOWS, and pediatricians are uniquely positioned to support mothers to manage their emotions while supporting the healing and development of their infants.[64] Nonpharmacologic care should also include a thorough assessment of the hospital environment and infant handling and adaptations by the infant to each to minimize NOWS expression.

Nonpharmacologic treatment may include a variety of supportive care approaches. As described by Velez and Jansson,[64] approaches to nonpharmacologic care should be tailored to the clinical behavioral and physiologic signs the infant is experiencing. Velez and Jansson[64] note 4 specific domains: (1) reactivity to sensory stimulation and regulatory issues, (2) behavioral states and state control, (3) motor and tone control, and (4) autonomic signs of stress. For example, an infant experiencing overreactivity to visual stimulation may benefit from a dimly lit environment, whereas an infant with hypertonia may benefit from swaddling (Fig 2).

Breastfeeding

Perhaps the most studied nonpharmacologic intervention is breastfeeding.[65] In general, breastfeeding is safe for mothers who take methadone or buprenorphine and may reduce clinical signs of NOWS and length of hospital stay; thus, in many settings, breastfeeding has become a critical foundation in care for the mother-infant dyad. Methadone and buprenorphine are excreted into human milk at low concentrations. The Academy of Breastfeeding Medicine has published consensus breastfeeding guidelines that suggest that breastfeeding should be encouraged if the mother has not had a relapse in >90 days but discouraged if there has been a relapse in the last 30 days.[66] Being HIV-positive is a contraindication to breastfeeding in high-income

countries, such as the United States, and HCV-positive mothers with bleeding or cracked nipples should also consider abstaining from breastfeeding.[67] Clinicians and patients should be cautious with sudden discontinuation of breastfeeding because some have reported signs of infant withdrawal.[68]

In a recent survey of women in treatment of OUD, it was found that although most mothers desire and attempt to establish breastfeeding, they encounter significant challenges (eg, long NICU stays, lack of support and education) that compromise their success. For these reasons, rates of breastfeeding initiation, exclusivity, and duration remain low among mothers with OUD. In addition, some mother-infant dyads may have difficulty with latching because of withdrawal and may require fortification of milk because of infant weight loss, which can lead to fewer breastfeeding attempts and lower sustainment of breastfeeding. Lastly, breastfeeding counseling and support should be trauma informed because mothers with OUD report high rates of trauma, including sexual trauma, which may influence their desire to breastfeed.[69–71]

PHARMACOTHERAPY

For infants with severe NOWS, use of a medication in addition to nonpharmacologic measures is necessary to improve clinical signs of withdrawal and minimize complications from withdrawal (eg, severe weight loss). Ideally, pharmacotherapy minimizes clinical signs of withdrawal, and then the infant is weaned off the medication using a standardized protocol to minimize total medication exposure.[72] Pharmacologic therapy should be considered for severe opioid withdrawal despite nonpharmacologic interventions. Vomiting and loose stools are associated with dehydration and poor weight gain and are relative indications for treatment. Naloxone should never be administered to an infant with NOWS because it will exacerbate the underlying withdrawal syndrome.

The literature supports the use of an opioid for opioid withdrawal as a first-line agent.[73] In the United States, the most common first-line therapy for NOWS is morphine.[61] In several recently published studies, it was found that longer-acting opioids may reduce length of stay when compared with morphine. Kraft et al[74] found that when compared with morphine, buprenorphine used for NOWS resulted in a shorter median duration of treatment (15 vs 18 days; $P < .001$) and length of hospital stay (21 vs 33 days; $P < .001$). Similarly, Davis et al[75] found that when compared with morphine, methadone resulted in a shorter duration of treatment (11.5 vs 15 days; $P = .009$) and length of stay (16 vs 20 days; $P = .005$). Importantly, both clinical trials occurred in the context of rigorous study protocols and included only women in treatment of OUD to test the efficacy of these medications; therefore, one limitation of these clinical trials may be generalizability to other populations (ie, infants of mothers not in treatment of OUD).

There is evidence to support the use of secondary medications for NOWS, either when initiating pharmacotherapy[76] or, more commonly, as an additional medication when clinical signs continue to escalate despite

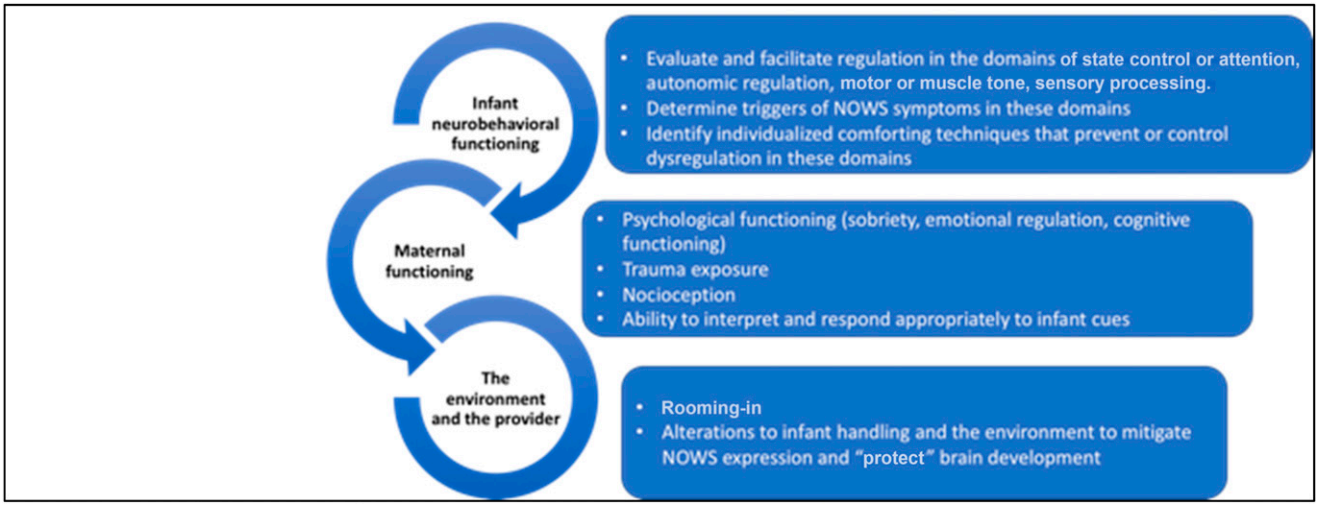

FIGURE 2

Nonpharmacologic approaches to NOWS. Adapted from Velez M, Jansson LM. The opioid dependent mother and newborn dyad: non-pharmacologic care. *J Addict Med.* 2008;2(3):113–120.

pharmacotherapy with an opioid. The most common medications used after initiation of an opioid for NOWS are clonidine and phenobarbital. The majority of practitioners use phenobarbital as a second drug if the opioid does not adequately control withdrawal signs.[77,78] In recent years, clonidine has increased in the United States as a therapy for NOWS.[61] Clonidine is an α-2-adrenergic receptor agonist that has been used in combination with an opioid or other drug in older children and adults to reduce withdrawal symptoms.[79,80] There is not sufficient evidence to suggest greater efficacy of clonidine over phenobarbital; however, phenobarbital has been shown to have neurotoxicity in animal studies,[81,82] and its use has been associated with adverse developmental outcomes.[83] Therefore, clinicians should consider use of clonidine as a second-line agent over phenobarbital, and additional study is needed to test the effects of both agents on infants' long-term development.

Clinicians should be mindful that some drug preparations may include a high alcohol content (eg, buprenorphine), and choosing preparations of low alcohol content is preferred. In addition, consistent with previous AAP statements, camphorated tincture of opium (paregoric) and/or deodorized tincture of opioid (laudanum) should not be used for NOWS.

PREPARING FOR DISCHARGE

It is important to plan effectively for a safe transition from the hospital to home after birth for the mother-infant dyad. Families of infants with opioid exposure are disproportionately impoverished,[28] may face multiple economic and social challenges,[12,25,84] and are frequently involved in the child welfare system. Adequate preparation for hospital discharge cannot be the pediatrician's responsibility alone; it requires hospital supports (eg, social work) to appropriately assess and assist families in this critical transition.

The immediate postnatal period is a time of high risk for mothers with OUD, especially if they lose access to medications for OUD. Recent data suggest that loss of access to medications for OUD after delivery is associated with overdose death.[85] In addition, a key support to give mothers the best chance of remission of OUD and improved dyadic relational health is partnering with mental health clinicians to provide comprehensive treatment. For example, maternal screening for treatable problems, such as traumatic stress and depression, could be addressed by referral to evidence-based, dyadic-focused interventions, such as child-parent psychotherapy.[86]

Infants with opioid exposure are also at risk for adverse outcomes, including hospital readmission.[87,88] Women may have to manage their own medical follow-up needs (eg, obstetrics, addiction medicine), their infant's medical follow-up needs (eg, general pediatrician, pediatric infectious disease, lactation support), and additional services (eg, the Special Supplemental Nutrition Program for Women, Infants, and Children, early intervention, child welfare). The task of coordinating these multiple stakeholders, combined with the risk of adverse postdischarge outcomes (such as readmission),[88] makes formalizing the discharge process for infants with opioid exposure critical. Use of simplified electronic or print checklists can be helpful in improving discharge processes (Table 4).[89] When possible, postdischarge care for the mother-infant dyad should be coordinated and comprehensive. Lastly, hospitals should ensure adequate handoffs and information transfer to postdischarge care providers, including, pediatricians, early intervention providers, and home-nurse visitation programs.

Discharge Education

In addition to routine newborn education, emphasis should be placed on the needs of the opioid-exposed dyad. Ideally, the infant caregiver has been engaged in care during the pregnancy and is familiar with common clinical signs and scoring processes. The caregiver should know when and how to seek help if signs of infant withdrawal become unmanageable or if additional challenges present (eg, maternal depression, relapse). Infants with substance exposure are at an increased risk of sleep-related deaths[90]; therefore, additional emphasis on safe sleep and safe sleep environments is recommended. Similar to all infant discharges, parents of infants with opioid exposure should be provided education on how to deal with challenging infant behaviors (eg, subacute withdrawal signs) that may increase the risk of nonaccidental trauma.

Medical Follow-up

Infants should be observed for 24 to 48 hours after finishing any medication taper. Ideally, an infant with opioid exposure would be seen by his or her pediatrician within 48 hours of discharge from the hospital to monitor for adequate weight gain and to monitor for any continued signs of withdrawal. The frequency of pediatrician visits may need to be higher than that for uncomplicated term infants. Although there are no data to inform the most optimal pediatrician visit schedule for infants with opioid exposure, the infant should be seen within 48 hours of discharge, with a 1-week follow-up. Additional visits should be tailored to the needs of the dyad. Ideally, breastfed infants should also have outpatient lactation support

TABLE 4 Discharge Checklist for Infants With Opioid Exposure

Completed (Check Yes)	Task
	No significant clinical signs of withdrawal for 24–48 h
	Parent education about NOWS and routine newborn care, emphasizing safe sleep
	Pediatrician or primary care provider follow-up visit scheduled within 48 h of discharge
	Early intervention services referral
	Home-nurse visitation referral
	Hepatitis C testing follow-up, including referral to pediatric infectious disease when appropriate
	Plan of safe care, coordinating with child welfare as appropriate
	Developmental-behavioral pediatrician referral as appropriate

and be assessed in the first 48 hours of life.

Outpatient Pharmacotherapy

With increasing focus on reducing length of hospital stay for infants with NOWS, many institutions began discharging infants from the hospital on medications. Among infants treated in the nearly 200 centers participating in the Vermont Oxford Network collaboration focused on improving care for NOWS, >25% were discharged from the hospital on medications at the end of the 2-year collaborative.[60] Consistently, the literature suggests that discharging infants from the hospital on pharmacotherapy reduces length of hospital stay[91–94]; however, comparative outcomes, in particular duration of total treatment and development outcomes, are scant. In a recent study, of nearly 1000 infants with NOWS enrolled in the Tennessee Medicaid program, infants discharged from the hospital on medications had a shorter median length of hospital stay (11 vs 23 days; $P < .001$) but longer median lengths of treatment (60 vs 19 days; $P < .001$).[87] Given the lack of long-term follow-up data, clinicians should avoid outpatient tapers when possible. If outpatient tapers are used, a structured weaning plan with comprehensive follow-up should be implemented to minimize total medication time.

Hepatitis C

HCV screening among pregnant women is not universal in the United States, potentially missing a window of opportunity to identify HCV in the mother-infant dyad. Even without universal screening, data suggest that as the opioid crisis grew, rates of HCV infection among pregnant women increased.[95] From 2009 to 2014, the rate of HCV infection among US pregnant women doubled to 3.4 per 1000 live births and as high as 1 in 50 births in West Virginia.[96] Given this rising risk to maternal and infant health, hospitals should consider universally screening pregnant women for HCV and creating processes to connect the dyad to treatment postnatally.

Because vertical transmission occurs in 6% of infants exposed to HCV (11% if HIV coinfection), infants must be tested after discharge to determine if they seroconvert. Maternal antibodies can persist for 18 months; thus, antibody testing must occur after 18 months; however, RNA polymerase chain reaction testing may occur earlier. Data suggest, however, that only a minority of exposed infants are tested.[97,98] Because infants with opioid exposure are at risk for HCV exposure, it is imperative that (1) all infants with opioid exposure are evaluated for HCV exposure and (2) all infants with HCV exposure are adequately managed to determine if they acquire the virus. All infants HCV exposure should be evaluated and should be tested for seroconversion by using RNA polymerase chain reaction or antibody testing.

Postdischarge Services

Infants with opioid exposure, regardless of the need for pharmacotherapy for NOWS, are at increased risk for developmental alterations.[99] In addition to developmental, behavioral, and mental health[100] screenings by the primary care pediatrician, all infants with substance exposure should be referred to early intervention services, and developmental screenings in a NICU developmental assessment clinic or equivalent should be considered. Early intervention services are available in all areas of the United States as part C of the Individuals with Disabilities Education Act. Strong consideration should also be given to referral to home-nurse visitation programs (eg, the Maternal, Infant, and Early Childhood Home Visiting Program) as a resource to families.

Early Head Start programs are similar to Head Start but are targeted to pregnant women and infants until age 3 years. These programs support parental and infant development and can further enable family success, promoting housing and financial stability. Pediatricians should consider referrals to Early Head Start programs for opioid-exposed infants. Early Head Start programs can be identified by using the Center Locator (https://eclkc.ohs.acf.hhs.gov/center-locator).

In addition, the AAP has several resources to aid pediatricians in connecting children to developmental resources that are free and available online, including the National Center on Early Childhood Health and Wellness (https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/NCECHW/Pages/National-Center-on-Early-Childhood-Health-and-Wellness.aspx) and publications such as *Caring for Our Children* (https://nrckids.org/CFOC/). Similar resources, such as HealthySteps (https://www.healthysteps.org/),

may also serve pediatricians in developing models of care to meet the needs of infants with opioid exposure.

The Child Welfare System and Plans of Safe Care

The opioid crisis resulted in greater demands on the US child welfare system.[12,13] Although evidence suggests that keeping the family intact improves outcomes for parents and infants, child safety must still be paramount.[12] A report to child protective services should be considered when the mother has not received or been adherent to treatment of OUD, when there is concern or evidence of polysubstance use during pregnancy, or when there is a concern for infant safety. In cases in which a child cannot be safely cared for by his or her parents, appropriately trained kinship or foster care placement may be necessary. Referral to child protective services is not a substitute for referral to treatment of the pregnant or parenting woman.

Recently, there have been numerous changes to the child welfare system to provide parental supports and connection to treatment. In 2016, the Comprehensive Addiction and Recovery Act amended the Child Abuse Prevention and Treatment Act to ensure that "plans of safe care" are created for infants "being affected by substance abuse or withdrawal symptoms, or a fetal alcohol spectrum disorder." Importantly, these plans should address the "health and substance use disorder treatment needs of the infant and affected family or caregiver."[101] Ideally, plans of safe care are well coordinated within state child welfare agencies, and planning begins before birth. States may interpret and implement legislation related to plans of safe care differently; therefore, it is important for pediatricians to be aware of their local requirements. The creation of plans of safe care are actively being developed, and there is evidence that many states are struggling with implementation.[13] Pediatricians should consider involvement in the development of plans of safe care in their communities. Because of their expansive nature of supporting the mother-infant dyad, some states have elected to call their plans of safe care "plans of supportive care." Such partnerships between pediatricians and child welfare professionals can help fill education gaps, foster positive partnerships, and promote understanding, with the ultimate goal of improving outcomes for the mother-infant dyad.[102]

Public Health Considerations

NOWS reflects the downstream implications of a complex public health crisis. To prevent NOWS, pregnant women, women and men of reproductive age, and the communities they live in need effective access to prevention, treatment, and services (eg, access to comprehensive treatment of substance use disorder, access to highly effective contraception) (Fig 3).[103,104] As public health and surveillance efforts continue to evolve, involvement of pediatricians at the local, state, and national level will continue to be important to ensure that the unique needs of children are addressed.

A federal prevention strategy outlined in the 2015 Protecting our Infants Act[105] provides several mandates for the US Department of Health and Human Services (HHS) to address problems related to prenatal opioid exposure. The strategy requires HHS agencies to plan, review, and coordinate activities related to prenatal opioid exposure and NOWS to (1) develop recommendations for prevention; (2) treat OUD in pregnant women and infants with NOWS; (3) identify pregnant women and infants in need of services to treat OUD in pregnancy and NOWS, including any long-term consequences; and (4) develop a coordinated strategy to address gaps in research. In fall 2018, the HHS held a summit to improve coordination of national surveillance, research, and prevention efforts.[106]

Currently, there is considerable variation in reporting of NOWS by state or jurisdiction. Improvement in reporting of NOWS to public health officials can help to identify communities in critical need of intervention. Currently, only a handful of states have mandatory reporting of NOWS,[107] and states vary in case definitions for state reporting. In a study of 6 states with case reporting for NOWS during 2013–2017, considerable variability was found in how states defined and used surveillance.[107] Nevertheless, for states and other jurisdictions to improve reporting, a consistent definition is needed. In an attempt to provide a more universal definition for public health surveillance, the Council on State and Territorial Epidemiologists, in collaboration with the Centers for Disease Control and Prevention, met with state health officials to improve reporting in all states on the basis of maternal opioid use reported in prenatal and delivery records as well as newborn hospitalization records.[108] With more consistent reporting, states may be able to better and more rapidly identify needs among and between localities.

State and regional collaborations are developing strategies to improve access to maternal medications for OUD, improve the quality of care for newborn infants with NOWS, and reduce hospital length of stay and associated costs. Ohio's Perinatal Quality Collaborative initiated a statewide approach to the care of infants with NOWS that included standardized assessment and treatment, including both pharmacologic and nonpharmacologic interventions.

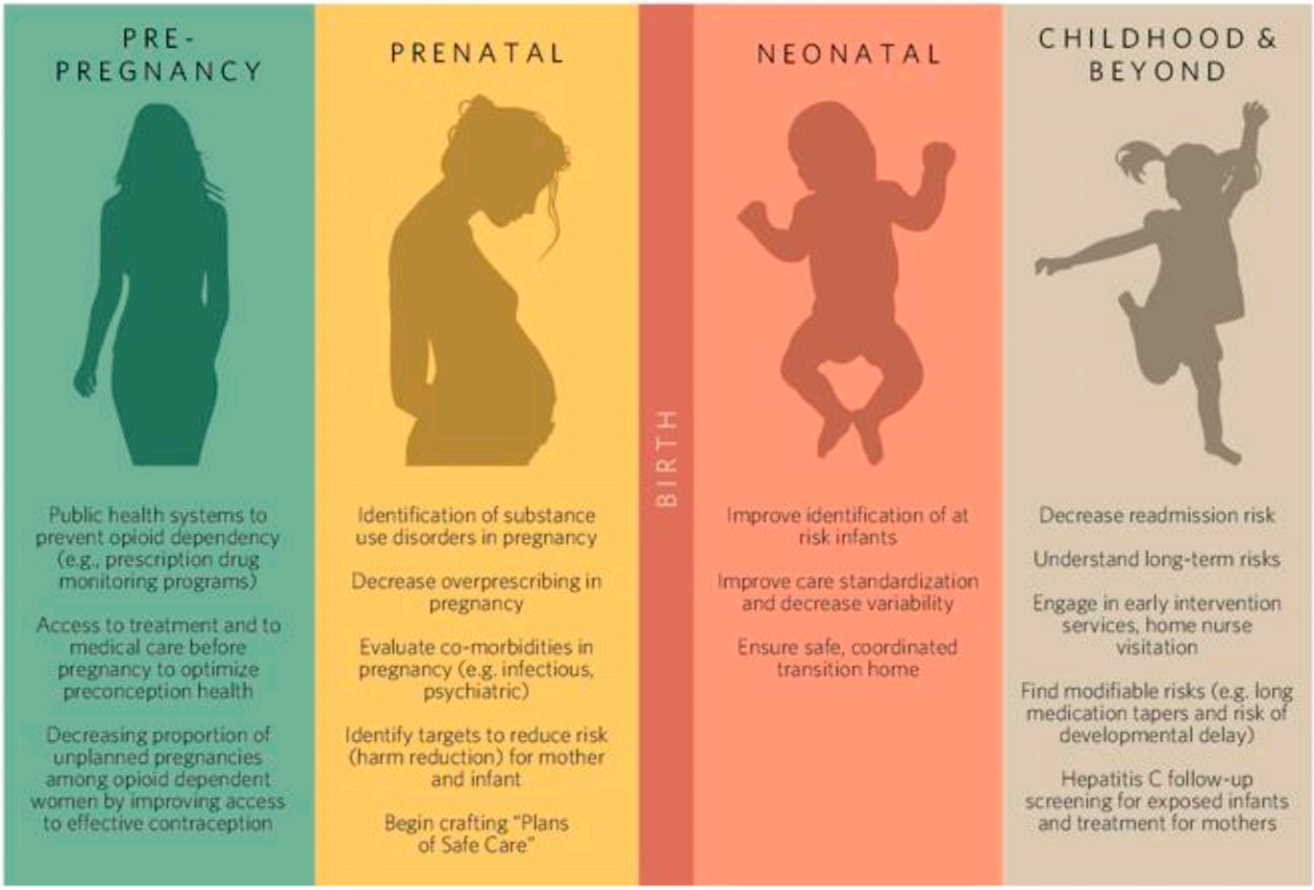

FIGURE 3
Public health approaches to opioid use in pregnancy and in infants with opioid exposure. (Reprinted with permission from Patrick SW. Improving public health systems for substance-affected pregnancies. *Am J Public Health*. 2019;109(1):22–23.)

Among 52 of the state's 54 neonatal care facilities, standardized pharmacologic treatment and increased use of nonpharmacologic treatment reduced both the length of treatment and the length of hospital stay from 13.4 to 12 days and from 18.3 to 17 days, respectively.[109] Among a multistate, multicenter quality improvement collaborative, participating hospitals were able to reduce the median length of pharmacologic treatment from 16 to 15 days and the infant length of hospital stay from 21 to 19 days through a standardized scoring process for NOWS. Albeit noteworthy, these reductions in length of stay and costs are modest. Additional quality improvement approaches and measures are needed to improve care to the mother-infant dyad.

CONCLUSIONS

The opioid crisis has had a profound effect on pregnant women and their infants. Despite improvements in the identification, assessment, and treatment of NOWS, substantial knowledge gaps remain. Pediatricians are well positioned to improve outcomes for the mother-infant dyad through evidence-based practice and connection of families to public resources.

RECOMMENDATIONS

NOWS is a major consequence of the opioid crisis, with dramatic increases over the last decade. Pediatric care clinicians can help reduce newborn morbidity, hospitalization, and costs and help improve maternal screening, referral, and follow-up for the mother-infant dyad. We present the following recommendations for care.

Access to Treatment

1. All pregnant women should have access to medications for OUD because they have been shown to reduce risk of overdose death and improve pregnancy outcomes.
2. Pediatricians should partner with state and local child welfare agencies to advocate for funding to improve access to quality treatment of OUD.

Antenatal Counseling and Screening

1. Pregnant women with OUD should receive antenatal counseling to provide education on the clinical signs of withdrawal and enhance maternal understanding of postnatal treatment (eg,

nonpharmacologic treatment, including breastfeeding and pharmacotherapy). When possible, maternal antenatal counseling should be provided by a pediatric provider.

2. Multiple modalities of testing should be considered for the infant, including, infant urine, meconium, and umbilical cord tissue testing.
3. For women in treatment of OUD who receive frequent toxicology testing, infant meconium and/or umbilical cord tissue testing may not be necessary.
4. For many substances, urine toxicology only captures a short window of substance use for some systems.
5. Pediatricians should assess additional social risks, including, but not limited to, food and housing insecurity, and connect to community resources.

Observation

1. All infants with chronic opioid exposure should be observed for at least 72 hours to monitor for the development of withdrawal. Although there is increasing evidence that multiple factors may increase an opioid-exposed infant's risk of withdrawal (eg, gestational age, specific genotypes, tobacco use, benzodiazepine, and gabapentin), there remains insufficient evidence of how to use these exposures to tailor an infant's postnatal observation period. Institutions may use the following approach for observation of infants with opioid exposure:
2. immediate-release opioids: 3 days;
3. buprenorphine and sustained-release opioids: 4 to 7 days; and
4. methadone: 5 to 7 days.

Diagnosis

1. For all infants at risk for NOWS, a standardized assessment approach by using a commonly used tool (eg, modified Finnegan score) should be employed to measure the presence and severity of withdrawal symptoms as well as the response to treatment (Fig 1).
2. Comorbidities should also be considered, including infectious and neurologic conditions. If no clear in utero exposure is identified through maternal history, screening, or testing, NOWS is a diagnosis that should be used only if other potential causes of an infant's symptoms have been evaluated fully and no other cause has been identified.

Treatment

1. Hospitals should prioritize keeping the mother-infant dyad intact throughout observation and treatment of an infant with opioid exposure. Rooming-in is the preferred model of care.
2. Hospitals should have a written protocol for the nonpharmacologic and pharmacologic treatment of an infant with opioid exposure.
3. Admission to a NICU only for opioid exposure or NOWS is not required.
4. All hospitals should have a written protocol for initiating nonpharmacologic and pharmacologic treatment of an infant with opioid exposure.
5. Nonpharmacologic interventions should be used for all infants with opioid exposure and should be considered the foundation of care.
6. Nonpharmacologic treatment should be tailored to the clinical signs of the infant.
7. All hospitals should have a protocol for breastfeeding an infant with substance exposure.
8. For infants of mothers in treatment of OUD with buprenorphine or methadone who have not had relapse for $\geq$90 days, breastfeeding should be supported if there are no other contraindications.
9. For infants of women with active substance use or with relapses within the last 30 days, breastfeeding should be discouraged.
10. For infants of women in treatment between 30 and 90 days without relapse, breastfeeding should be considered.
11. HIV is a contraindication to breastfeeding in high-income countries, such as the United States. HCV-positive mothers with cracked or bleeding nipples should consider abstaining from breastfeeding.
12. Lactation support should be provided in the inpatient setting and after discharge.
13. Pharmacologic therapy should be considered for severe opioid withdrawal (eg, MOTHER score $>8 \times 2$ or $>12 \times 1$) in addition to nonpharmacologic interventions. Vomiting and loose stools are associated with dehydration and poor weight gain and are relative indications for treatment.
14. Opioids should be used as a first-line therapy for severe NOWS.
15. Infants who require pharmacologic treatment should be monitored (eg, pulse oximetry).
16. Recent data suggest that opioids with a longer half-life, such as buprenorphine and methadone, may reduce length of treatment. However, caution should be considered if the preparation has a high alcohol content.
17. Paregoric and deodorized tincture of opium should not be used.
18. If a second agent is needed for severe opioid withdrawal, the use of clonidine should be considered over phenobarbital.

19. Naloxone should never be used in the treatment of an infant with chronic opioid exposure because it may precipitate rapid withdrawal and seizure.

Discharge

1. Discharge of infants from the hospital on pharmacotherapy should be avoided and should only occur if there is a structured, close outpatient follow-up plan for the mother-infant dyad.
2. A discharge checklist should be completed (Table 3):
3. no significant clinical signs of withdrawal for 24 to 48 hours after treatment;
4. parent education about NOWS and routine newborn care, emphasizing safe sleep;
5. pediatrician or primary care provider follow-up visit with 48 hours of discharge;
6. early intervention services referral;
7. consideration of home-nurse visitation and Early Head Start;
8. hepatitis C and HIV testing referral, including referral to pediatric infectious disease when appropriate;
9. plan of safe care, coordinating with child welfare;
10. developmental-behavioral pediatrician referral, as appropriate; and
11. consideration of behavioral and/or mental health system referrals to address dyadic relational health.

LEAD AUTHORS

Stephen W. Patrick, MD, MPH, MS, FAAP
Wanda D. Barfield, MD, MPH, FAAP
Brenda B. Poindexter, MD, MS, FAAP

COMMITTEE ON FETUS AND NEWBORN, 2019–2020

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LIAISONS

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Michael Narvey, MD – *Canadian Paediatric Society*
Russell Miller, MD – *American College of Obstetricians and Gynecologists*
RADM Wanda Barfield, MD, MPH, FAAP – *Centers for Disease Control and Prevention*
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Stephen W. Patrick, MD, MPH, MS, FAAP
Joanna Quigley, MD, FAAP
Sheryl A. Ryan, MD, FAAP
Leslie Walker-Harding, MD, FAAP

LIAISON

Rebecca Ba'Gah, MD – *American Academy of Child and Adolescent Psychiatry*

STAFF

Renee Jarrett, MPH

ABBREVIATIONS

AAP: American Academy of Pediatrics
ACOG: American College of Obstetricians and Gynecologists
CI: confidence interval
ESC: Eat, Sleep, Console
HCV: hepatitis C virus
HHS: US Department of Health and Human Services
MOTHER: Maternal Opioid Treatment: Human Experimental Research
NOWS: neonatal opioid withdrawal syndrome
OUD: opioid use disorder

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